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Role of Clopidogrel Loading Dose in Patients With ST-Segment Elevation Myocardial Infarction Undergoing Primary Angioplasty

Results From the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) Trial

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Objectives Our aim was to determine whether a 600-mg loading dose of clopidogrel compared with 300 mg results in improved clinical outcomes in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI).

Background A 600-mg loading dose of clopidogrel compared with 300 mg provides more rapid and potent inhibition of platelet activation.

Methods In the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial, 3,602 patients with STEMI undergoing primary PCI were randomized to bivalirudin (n = 1,800) or unfractionated heparin plus a glycoprotein IIb/IIIa inhibitor (n = 1,802). Randomization was stratified by thienopyridine loading dose, which was determined before random assignment.

Results Patients in the 600-mg (n = 2,158) compared with the 300-mg (n = 1,153) clopidogrel loading dose group had significantly lower 30-day unadjusted rates of mortality (1.9% vs. 3.1%, p = 0.03), reinfarction (1.3% vs. 2.3%, p = 0.02), and definite or probable stent thrombosis (1.7% vs. 2.8%, p = 0.04), without higher bleeding rates. Compared with unfractionated heparin plus a glycoprotein IIb/IIIa inhibitor, bivalirudin monotherapy resulted in similar reductions in net adverse cardiac event rates within the 300-mg (15.2% vs. 12.3%) and 600-mg (10.4% vs. 7.3%) clopidogrel loading dose subgroups ($p_{interaction}$ = 0.41). By multivariable analysis, a 600-mg clopidogrel loading dose was an independent predictor of lower rates of 30-day major adverse cardiac events (hazard ratio: 0.72 [95% confidence interval: 0.53 to 0.98], p = 0.04).

Conclusions In patients with STEMI undergoing primary PCI with contemporary anticoagulation regimens, a 600-mg loading dose of clopidogrel may safely reduce 30-day ischemic adverse event rates compared with a 300-mg loading dose. (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction [HORIZONS-AMI]; NCT00433966) (J Am Coll Cardiol 2009;54:1438–46) © 2009 by the American College of Cardiology Foundation

Greater platelet inhibition is associated with a reduced risk of ischemic events in patients undergoing percutaneous coronary intervention (PCI) with stents (1–9). Insufficient platelet inhibition may be especially problematic when PCI is performed in the thrombogenic milieu of patients with acute coronary syndromes (ACS) (10). Several studies have

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investigated the optimal clopidogrel loading dose in patients with stable angina and non–ST-segment elevation myocardial infarction undergoing PCI (11–14). In these studies, a 600-mg loading dose of clopidogrel consistently led to greater platelet inhibition compared with 300 mg (11,13,14). A 300-mg clopidogrel loading dose followed by 75 mg daily in addition to aspirin has also proven beneficial over aspirin alone in patients with acute myocardial infarction (MI) treated with fibrinolytic therapy (15,16). Neither loading dose of clopidogrel has been studied in patients with acute MI undergoing primary PCI.

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In the multicenter prospective, randomized HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial (17), 3,602 ST-segment elevation myocardial infarction (STEMI) patients undergoing a primary PCI strategy were randomly assigned to either unfractionated heparin (UFH) plus glycoprotein IIb/IIIa inhibitors (GPIs) or bivalirudin monotherapy after stratification according to thienopyridine loading dose. In the present study, we evaluated the impact of clopidogrel loading with 600 mg versus 300 mg on 30-day clinical outcomes.

Methods

Patient population and study protocol. The HORIZONS-AMI trial design has been described elsewhere (17). In brief, this study was a prospective, open label, 2 × 2 factorial randomized multicenter trial of 3,602 patients enrolled at 123 centers worldwide. The study protocol was approved by the institutional review board or ethics committee at each center, and written informed consent was obtained from all patients. Patients were randomized 1:1 in the emergency room to either administration of anticoagulation with UFH plus routine use of a GPI or bivalirudin plus bail-out GPI use reserved for refractory no-reflow or giant thrombus. After angiography, patients with lesions eligible for stenting then underwent a second randomization (3:1) to either Taxus Express-2 paclitaxel-eluting stents or otherwise identical uncoated Express-2 bare-metal stents (both Boston Scientific, Natick, Massachusetts). UFH was administered intravenously as a 60-IU/kg bolus with subsequent boluses to achieve an activated clotting time of 200 to 250 s. Bivalirudin was administered intravenously as a 0.75-mg/kg bolus plus infusion of 1.75 mg/kg/h. Aspirin (100 to 324 mg orally or 500 mg intravenously) was administered daily during the index hospitalization, and 75 to 100 mg/day was prescribed indefinitely after discharge. GPI treatment with either abciximab (0.25 mg/kg bolus plus 0.125 μg/kg/min infusion, maximum 10 μg/min) or double-bolus eptifibatide (180 μg/kg bolus plus 2.0 μg/kg/min infusion, with a second bolus given in 10 min) was permitted per investigator discretion, adjusted for renal impairment per Food and Drug Administration label, and continued for 12 h (abciximab) or 12 to 18 h (eptifibatide).

The initial loading dose of thienopyridine was left to the investigator's discretion, although at least a 300-mg clopidogrel loading dose was required to be administered in the emergency room per the trial protocol. Clopidogrel (75 mg/day) was mandated for ≥6 months (≥1 year recommended) after discharge. Ticlopidine was permitted in the case of clopidogrel allergy or unavailability.

The primary randomization was stratified by whether the patient was to be loaded with 300 mg of clopidogrel, 600 mg of clopidogrel, or 500 mg of ticlopidine before catheterization.

Abbreviations and Acronyms

ACS = acute coronary syndromes
CABG = coronary artery bypass grafting
GPI = glycoprotein IIb/IIIa inhibitor
MACE = major adverse cardiovascular events
MI = myocardial infarction
NACE = net adverse clinical events
PCI = percutaneous coronary intervention
STEMI = ST-segment elevation myocardial infarction
UFH = unfractionated heparin

Clinical end points and definitions. The primary end point definitions have been previously detailed (17). Composite major adverse cardiovascular events (MACE) (including death from any cause, stroke, reinfarction, and unplanned revascularization for ischemia) and major bleeding were adjudicated by an independent clinical events committee blinded to treatment assignment with review of original source documents. Net adverse clinical events (NACE) were defined as the occurrence of MACE or major bleeding unrelated to coronary artery bypass grafting (CABG).

Statistical analysis. Continuous variables were expressed as median and interquartile range and were compared using Wilcoxon rank sum test. Categorical variables were compared with the chi-square test or Fisher exact test. Cox proportional hazards regression was performed to identify the predictors of 30-day MACE and major bleeding unrelated to CABG. Interactions were tested by including the cross product of the 2 variables (an interaction term) in the Cox model. The multivariable model was built by stepwise variable selection with entry and exit criteria set at the $p = 0.1$ level. The following patient level candidate predictors were evaluated: age, women, height, weight, hypertension, hyperlipidemia, smoking, diabetes, family history of pre-mature coronary artery disease, previous MI, previous PCI, previous CABG, previous angina, previous congestive heart failure, history of peripheral vascular disease, baseline Killip class 1, baseline thrombocytopenia, baseline anemia (defined as baseline hematocrit below 39% for men and 36% for women), creatinine clearance, number of diseased vessels, baseline Thrombolysis In Myocardial Infarction flow grade, worst diameter stenosis, U.S. site, use of heparin pre-randomization, planned use of GPI, study medication started in emergency room versus cath lab, medi-

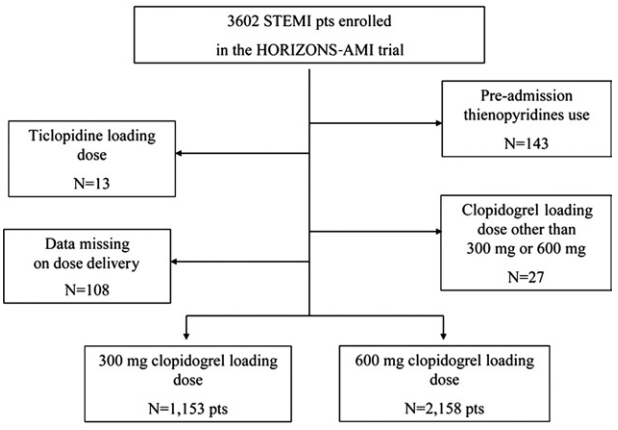

Figure 1 Flow Chart of the Present Study

Enrollment and follow-up of the patients (pts) in the trial. HORIZONS-AMI = Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction; STEMI = ST-segment elevation myocardial infarction.

cation use in the past 5 days at home (aspirin, beta-blocker, thienopyridines, calcium blocker, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, sildenafil citrate, diuretics, digoxin, hormone replacement therapy, amiodarone, or cyclooxygenase-2 inhibitor), randomization arm (bivalirudin vs. heparin plus GPI), and 300- versus 600-mg loading dose of clopidogrel. Clopidogrel loading dose was forced into the multivariable model as an entry criteria since it is the variable of interest for MACE and bleeding. For major bleeding predictors, intra-aortic balloon pump and closure device use were also added to the multivariate model, since in previous studies they have been associated with bleeding post-PCI.

In order to adjust for potential selection biases and potential confounding, patients in the 300 mg and 600 mg clopidogrel groups were matched using propensity scores (18). A logistic regression model was fit relating clopidogrel group (600 mg vs. 300 mg) to pre-treatment patient characteristics. Patients were then matched based on the resulting propensity score using the Caliper matching algorithm and the SAS "GREEDY" macro (SAS Institute, Cary, North Carolina). Outcomes were then modeled in this matched subset. All statistical tests were 2-tailed. Statistical significance was set at a level of 0.05.

Results

Patient characteristics. Of 3,602 patients enrolled in the HORIZONS-AMI trial, 291 patients were excluded from the present study, including 143 patients treated with thienopyridines before the randomization, 13 pa-

Table 1 Baseline Characteristics According to Clopidogrel Loading Dose

	300-mg Loading Dose (n = 1,153)	600-mg Loading Dose (n = 2,158)	p Value
Age (yrs), median (IQR)	60.5 (52.9–70.5)	60.1 (52.2–69.3)	0.14
Men	75.5%	76.9%	0.39
Body mass index (kg/m^2), median (IQR)	27.1 (24.6–30.1)	27.0 (24.5–30.3)	0.50
Hypertension	51.9%	52.7%	0.63
Hyperlipidemia	41.5%	42.4%	0.62
Current smoking	43.4%	47.4%	0.03
Diabetes mellitus	17.6%	15.6%	0.13
Insulin requiring	3.7%	4.5%	0.27
Anemia*	9.4%	10.7%	0.25
History of prior myocardial infarction	9.6%	9.8%	0.89
History of prior PCI	8.5%	9.4%	0.39
History of prior CABG	2.3%	2.9%	0.26
History of peripheral vascular disease	3.9%	4.5%	0.46
History of congestive heart failure	2.3%	2.9%	0.26
History of renal insufficiency†	2.9%	3.1%	0.86
Creatinine clearance (ml/min), median (IQR)	86.8 (66.0–113.9)	90.5 (69.6–114.3)	0.02
Platelet count ($\times$ 10^3 cells/mm^3), median (IQR)	250.5 (210.0–299.0)	245.0 (207.0–287.0)	0.02
Killip class 2 to 4	11.5%	6.9%	<0.0001
LVEF <40%	15.1%	13.7%	0.28
Symptom onset to hospital emergency unit (h), median (IQR)	2.2 (1.3–4.0)	2.2 (1.3–3.8)	0.31
Randomization			
UFH plus a GPI	50.7%	49.2%	0.44
Bivalirudin monotherapy	49.3%	50.8%	0.44

*Anemia is defined as baseline hematocrit <39 for men and <36 for women; †renal insufficiency was defined as a calculated creatinine clearance rate of <60 ml/min as determined by the Cockcroft-Gault equation.

CABG = coronary artery bypass graft surgery; GPI = glycoprotein IIb/IIIa inhibitor; IQR = interquartile range; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; UFH = unfractionated heparin.

tients loaded with ticlopidine, 27 patients who were treated with a clopidogrel loading dose other than 300 or 600 mg, and 108 patients without thienopyridine loading dose data (Fig. 1). The present study cohort was thus composed of 3,311 patients, including 1,153 patients who received a 300-mg loading dose of clopidogrel and 2,158 patients who received a 600-mg loading dose of clopidogrel before cardiac catheterization. Baseline clinical characteristics were generally well matched between the 2 groups except for higher prevalence of current smoking, Killip class 1 on presentation, higher baseline creatinine clearance, and lower platelet count in the 600-mg compared with the 300-mg group (Table 1). Additionally, patients in the 600-mg group were more likely to be treated with the femoral approach and with a closure device, but less likely to have a central venous access and intra-aortic balloon pump use (Table 2).

Clinical outcomes. By univariate analysis, the 30-day rates of mortality, reinfarction, MACE, and non–CABG-related major bleeding were significantly lower in the 600-mg clopidogrel loading dose group compared with the 300-mg loading dose group (Table 3, Fig. 2). The incidence of acquired thrombocytopenia was similar between the 2 groups. Among patients treated with PCI and coronary stent implantation, definite or probable stent thrombosis was also significantly lower among patient in the 600-mg compared with the 300-mg loading dose group (1.7% vs. 2.8%, $p = 0.04$).

Effect of clopidogrel loading dose within each randomization arm. As shown in Figure 3, the unadjusted rates of NACE, major bleeding, and MACE tended to be lower with the 600-mg compared with the 300-mg clopidogrel loading dose in both the heparin plus GPI and bivalirudin monotherapy arms. In this regard, there was no signifi-

Table 2 Procedural Characteristics According to Clopidogrel Loading Dose

	300-mg Loading Dose (n = 1,153)	600-mg Loading Dose (n = 2,158)	p Value
GPI administered	55.2%	54.1%	0.54
Diagnostic catheterization			
Femoral artery access	87.3%	96.7%	<0.0001
Radial artery access	12.4%	2.9%	<0.0001
Venous access obtained	10.1%	8.0%	0.03
Primary management strategy			
Primary PCI	93.2%	94.5%	0.13
Deferred PCI	0.2%	0.1%	1.00
CABG without PCI	1.8%	1.1%	0.09
Medical management only	4.8%	4.2%	0.46
PCI cohort	n = 1,077	n = 2,043	
Symptom onset to first balloon inflation (h), median (IQR)	3.9 (2.8–5.8)	3.6 (2.6–5.5)	0.0003
1 or more stents implanted, median (IQR)	95.6%	96.3%	0.31
Number of stents implanted	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.06
Total stent length implanted	24.0 (20.0–36.0)	24.0 (18.0–36.0)	0.008
Multiple vessels treated	4.5%	4.1%	0.68
Multiple lesions treated	9.9%	11.3%	0.26
Closure device	20.3%	33.2%	<0.0001
Intra-aortic balloon pump use	6.5%	4.8%	0.04
Index PCI vessels			
Left anterior descending	41.9%	40.3%	0.38
Left circumflex	15.5%	15.8%	0.80
Right coronary artery	40.6%	42.6%	0.28
Left main coronary artery	0.7%	0.5%	0.41
Saphenous vein graft	1.2%	0.8%	0.25
Internal mammary artery	0.1%	0.0%	0.35
TIMI flow grade pre-PCI*			
0/1	62.4%	59.3%	0.09
2	14.2%	13.5%	0.57
3	23.3%	27.1%	0.02
Final TIMI flow grade after PCI*			
0/1	2.6%	2.8%	0.70
2	12.3%	9.7%	0.02
3	85.1%	87.5%	0.06

*Core laboratory angiographic assessment.
TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Table 1.

Table 3 30-Day Clinical Outcomes According to Clopidogrel Loading Dose

	300-mg Loading Dose (n = 1,153)	600-mg Loading Dose (n = 2,158)	p Value
NACE	14.3%	9.0%	<0.0001
MACE	7.0%	4.3%	0.001
Death	3.1%	2.0%	0.03
Cardiac	2.7%	1.9%	0.11
Noncardiac	0.4%	0.1%	0.04
Reinfarction	2.6%	1.4%	0.01
Q-wave	1.6%	1.1%	0.27
Non–Q-wave	1.0%	0.3%	0.02
Death or reinfarction	5.4%	3.1%	0.001
Stroke	1.0%	0.5%	0.13
Ischemic target vessel revascularization	2.7%	1.9%	0.11
Stent thrombosis, ARC definite or probable	3.1%	2.0%	0.05
Bleeding			
Major bleeding (non–CABG-related)	9.4%	6.1%	0.0005
Major bleeding (including CABG)	11.4%	7.5%	0.0002
Minor bleeding	13.8%	11.3%	0.03
TIMI bleeding, any	10.2%	6.4%	<0.0001
Minor	5.7%	2.2%	<0.0001
Major	4.6%	3.6%	0.14
GUSTO bleeding, any	11.6%	7.6%	0.0001
Severe/life-threatening	0.6%	0.4%	0.45
Moderate	5.1%	3.3%	0.01
Mild	6.2%	3.9%	0.003
Severe/life-threatening/moderate	5.4%	3.6%	0.02
Thrombocytopenia ($\times 10^3$ cells/mm^3)			
Platelet count <10,0000	3.5%	2.9%	0.34
Platelet count <50,000	0.8%	0.9%	0.66
Platelet count <20,000	0.3%	0.3%	1.00

ARC = Academic Research Consortium; CABG = coronary artery bypass graft surgery; GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; MACE = major adverse cardiac events: death, reinfarction, target vessel revascularization, or stroke; NACE = net adverse clinical events: major adverse cardiac events or major bleeding (non–coronary artery bypass graft surgery-related); TIMI = Thrombolysis In Myocardial Infarction.

cant interaction between the randomization arm and clopidogrel loading dose group (p values for interaction = 0.48 for NACE, 0.41 for major bleeding, and 0.75 for MACE). Outcomes of the primary randomization to bivalirudin versus heparin plus GPI within the subsets of patients receiving either 600 mg or 300 mg clopidogrel loading dose are shown in Figure 4.

Multivariable analysis. Independent predictors of MACE and major bleeding unrelated to CABG at 30 days by multivariable analysis are listed in Table 4. A 600-mg rather than a 300-mg loading dose of clopidogrel was an independent predictor of 30-day MACE (hazard ratio: 0.72 [95% confidence interval: 0.28 to 0.6]; p = 0.04), but not of major bleeding.

Propensity score-matched patients. A total of 2,254 matched cases, 1,127 in each of the clopidogrel 300- and 600-mg groups were found. Results were similar to the main analysis in the full cohort; Table 5 summarizes the independent predictors of MACE and major bleeding at 30 days among propensity score-matched patients. A 600-mg rather than a 300-mg loading dose of clopidogrel remained an independent predictor of 30-day MACE after propensity score matching (hazard ratio: 0.67 [95% confidence interval: 0.47 to 0.96]; p = 0.03).

Discussion

The present study represents the first large report examining the impact of a 600-mg versus a 300-mg loading dose of clopidogrel on the clinical outcomes of patients with STEMI undergoing primary PCI. The major findings of the present study are that in patients with STEMI undergoing primary PCI: 1) a 600-mg compared with a 300-mg loading dose of clopidogrel was associated with lower 30-day rates of mortality, reinfarction, and stent thrombosis, and was, by multivariable analysis, an independent predictor of freedom from 30-day MACE; 2) the 600-mg loading dose was not associated with increased rates of major bleeding or thrombocytopenia; and 3) compared with heparin plus a GPI, the clinical benefits of bivalirudin monotherapy in reducing major bleeding and NACE were independent of the loading dose of clopidogrel, although overall adverse event rates were lower after a 600-mg loading dose than a 300-mg loading dose with both anticoagulation regimens.

Clopidogrel is well established for use in patients with ACS at a loading dose of 300 mg followed by a maintenance dosage of 75 mg/day. At this loading dose, inhibition of platelet aggregation is approximately 30% to 40%, and the time to peak effect is approximately 4 to 6 h. Several studies have shown greater inhibition with faster onset of action with a 600-mg compared with a 300-mg clopidogrel loading dose, which may be important in patients with STEMI in whom the duration from thienopyridine administration to PCI is abbreviated (3,9). Increasing the dosage from 300 to 600 mg increases the platelet aggregation inhibition to over 40% and significantly reduces the incidence of clopidogrel hyporesponsiveness. Delays in drug absorption

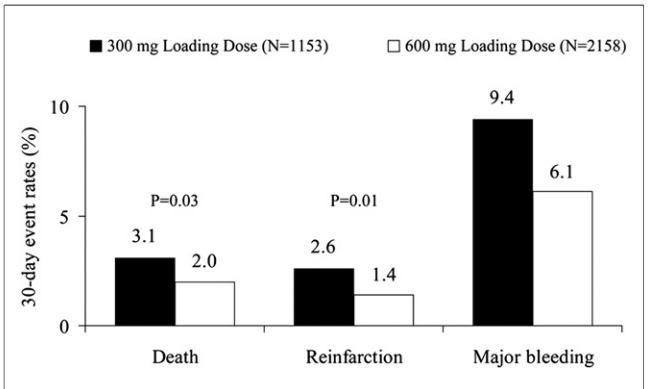

Figure 2 30-Day Clinical Outcomes

Subgroup analysis for the 30-day rates of death, reinfarction, and major bleeding according to clopidogrel loading dose. p = 0.0005.

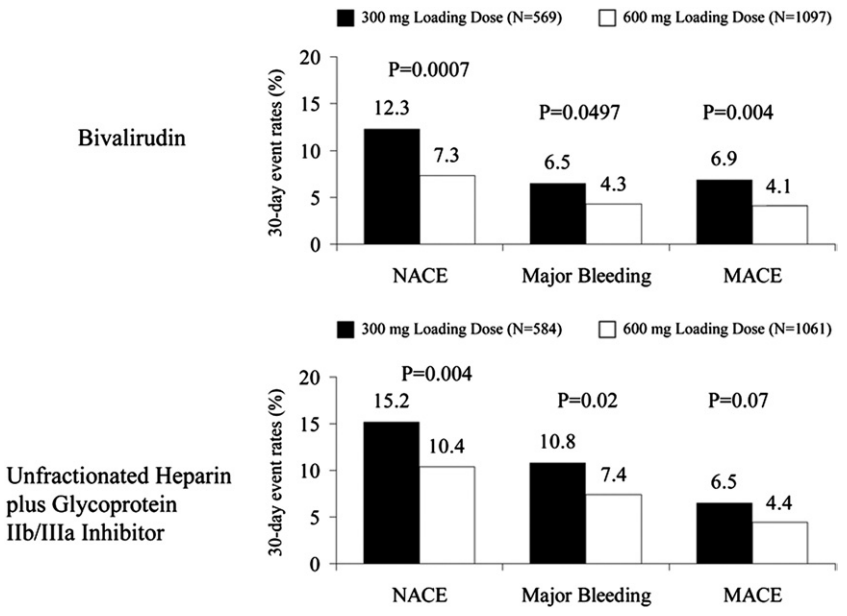

Figure 3 **Clinical Outcomes at 30 Days According to Stratification**

Clinical outcomes according to clopidogrel loading dose stratified treatment within the bivalirudin monotherapy and the unfractionated heparin plus glycoprotein IIb/IIIa inhibitor arms. MACE = major adverse cardiac events; NACE = net adverse clinical events.

and/or metabolism in the acute MI setting may further affect drug pharmacokinetics and pharmacodynamics. The clinical utility of the 600-mg clopidogrel loading dose in acute MI has been controversial, despite a meta-analysis of studies in PCI patients without acute MI that demonstrated significant benefits of this dose (19). The ARMYDA-2 (Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty) study reported that when administered 4 to 8 h before PCI in the nonurgent setting, a 600-mg clopidogrel loading dose was more effective than 300 mg in preventing periprocedural myonecrosis (14), although a benefit of the higher loading dose was not demonstrated in patients with stable angina undergoing PCI from a recently reported randomized trial or a large single-center experience (20,21). In patients with non–STEMI undergoing PCI, superior efficacy of a 600-mg compared with 300-mg clopidogrel loading dose has been demonstrated in 2 small studies (11,12). The present study extends the findings from these reports in demonstrating the utility of a 600-mg loading dose of clopidogrel in patients with STEMI in whom the time from clopidogrel administration to PCI is typically <90 min. By both multivariable and propensity score adjustment, the higher clopidogrel loading dose was a significant predictor of freedom from MACE at 30 days,

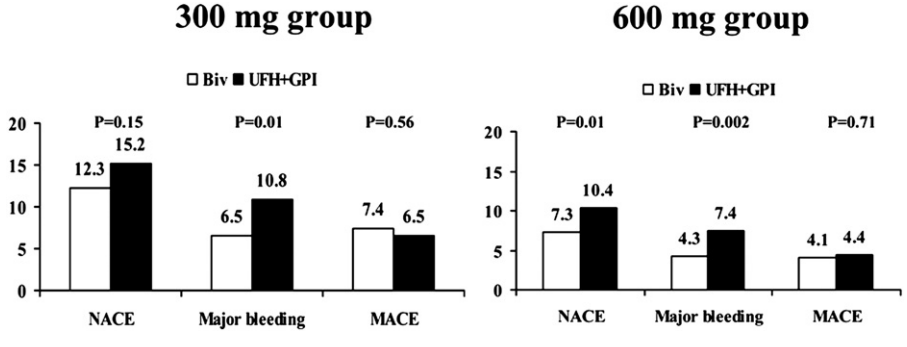

Figure 4 **Clinical Outcomes at 30 Days According to Randomized Assignments**

Clinical outcomes according to randomization to bivalirudin (Biv) monotherapy versus unfractionated heparin (UFH) plus glycoprotein IIb/IIIa inhibitor (GPI) within the groups of 600- and 300-mg clopidogrel loading doses. Abbreviations as in Figure 3.

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Table 4 Independent Predictors of 30-Day Clinical Events in the Full Cohort

	Hazard Ratio	95% CI	p Value
MACE			
Killip class 1	0.41	0.28–0.6	<0.001
Clopidogrel 600-mg loading dose	0.72	0.53–0.98	0.04
Platelet count ($\times 10^3$ cells/mm^3)	1.002	1.00–1.004	0.03
Age	1.03	1.02–1.05	<0.001
U.S. site	1.49	1.07–2.08	0.02
History of CHF	1.76	0.94–3.27	0.076
History of peripheral vascular disease	1.87	1.12–3.12	0.02
Major bleeding			
Randomization to bivalirudin	0.57	0.43–0.75	<0.001
Killip class 1	0.63	0.44–0.91	0.01
Creatinine clearance (ml/min)	0.99	0.98–0.99	0.002
Female sex	1.45	1.08–1.93	0.01
Anemia at baseline	1.62	1.13–2.32	0.008
U.S. site	2.44	1.84–3.23	<0.001
Intra-aortic balloon pump use	3.53	2.49–5.01	<0.001
Closure device	0.80	0.57–1.11	0.17
Clopidogrel 600-mg loading dose	0.87	0.66–1.14	0.30

CHF = congestive heart failure; CI = confidence interval; MACE = major adverse cardiac events: death, reinfarction, target vessel revascularization, or stroke.

and was associated with lower death, reinfarction, and stent thrombosis rates.

Of note, in the present study, the 600-mg compared with the 300-mg loading dose of clopidogrel was not associated with greater rates of major bleeding, even after multivariable analysis. Indeed, a trend toward a lower adjusted rate of bleeding complications was evident with the higher 600-mg loading dose. A similar trend was reported from an analysis of the combined GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) I and III studies, which demonstrated that higher initial aspirin doses (163 to 330 mg) were associated with less in-hospital bleeding compared with lower aspirin doses in patients with STEMI treated with fibrinolytic therapy (22). The higher use of intra-aortic balloon pump and venous access could explain the higher bleeding rates in the 300-mg group in the present study (Table 2); by multivariate analysis, intra-aortic balloon pump was a predictor of bleeding whereas the clopidogrel dose was not.

In the present study, the clinical advantages of the 600-mg compared with the 300-mg clopidogrel loading dose were observed in patients treated with UFH plus GPI as well as with bivalirudin monotherapy. Prior studies have described that the administration of larger (>300 mg) oral loading doses of clopidogrel may accelerate the time course and enhance the magnitude of subsequent platelet inhibition as well as reduce platelet reactivity in patients receiving GPI (23,24). In patients receiving UFH without GPI, significantly greater inhibition of adenosine diphosphate-induced platelet activation has been reported with a 600-mg compared with a 300-mg clopidogrel loading dose within 2 to 3 h after administration (23,25), an effect that persists for 48 h (26). Whether the same applies for bivalirudin-treated patients has not been studied. Moreover, the relevance of these studies in patients with ACS and STEMI is uncertain, because these patients have increased baseline indexes of platelet activation compared with patients without ACS (10), and primary PCI is often completed well under 2 h from clopidogrel administration. The present study suggests that the benefits of clopidogrel in patients undergoing an early invasive strategy may be enhanced by increasing the loading dose to 600 mg. This hypothesis is being further tested in the CURRENT-OASIS 7 (Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent EveNTs-Optimal Antiplatelet Strategy for InterventionS) trial in which patients with ACS are randomized to a 600-mg dose regimen of clopidogrel versus the standard dose regimen of 300-mg loading dose followed by 75 mg daily.

Importantly, the previously reported beneficial effects of bivalirudin compared with UFH plus GPI in reducing NACE and major bleeding while affording similar rates of MACE in patients with STEMI undergoing primary PCI (17) were independent of clopidogrel loading dose, although the overall adverse event rates were lower after a 600-mg loading dose with both anticoagulation regimens. Of note, even after a 600-mg clopidogrel loading dose, the full antiplatelet effect of the drug is achieved only after 2 h, and with wide individual variability (27). This observation suggests that a faster acting and more potent agent might further enhance the clinical benefit of early platelet inhibition before primary PCI in STEMI. Prasugrel, a novel thienopyridine antiplatelet agent, has a more rapid onset of action and is more potent than clopidogrel (>80% inhibi-

Table 5 Independent Predictors of 30-Day Clinical Events Among Propensity-Matched Patients*

	Hazard Ratio	95% CI	p Value
MACE			
Killip class 1	0.36	0.24–0.55	<0.001
Clopidogrel 600-mg loading dose	0.67	0.47–0.96	0.03
Platelet count ($\times 10^3$ cells/mm^3)	1.002	1.00–1.004	0.021
Age	1.04	1.02–1.05	<0.001
U.S. site	1.46	1.01–2.12	0.045
History of CHF	1.60	0.70–3.67	0.27
History of peripheral vascular disease	2.04	1.14–3.64	0.016
Major bleeding			
Randomization to bivalirudin	0.58	0.43–0.78	0.0004
Killip class 1	0.58	0.39–0.86	0.0072
Creatinine clearance (ml/min)	0.99	0.98–0.99	<0.0001
Women	1.53	1.10–2.11	0.01
Anemia at baseline	1.82	1.21–2.74	0.0043
U.S. site	2.37	1.73–3.25	<0.001
Intra-aortic balloon pump use	3.50	2.37–5.16	<0.001
Closure device	0.85	0.58–1.24	0.39
Clopidogrel 600-mg loading dose	0.90	0.66–1.20	0.47

*A total of 2,254 matched cases, 1,127 patients each treated with clopidogrel 300 mg and 600 mg.

Abbreviations as in Table 4.

tion of platelet aggregation) (28). In the TRITON–TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction 38) trial, randomization of 3,354 patients with acute or recent STEMI undergoing PCI to a 60-mg prasugrel load rather than a 300-mg clopidogrel load each followed by a daily maintenance dosage over 15 months resulted in a significant reduction in the composite end point of cardiovascular death, MI, or stroke at 30 days and 15 months as well as higher rate of bleeding in patients who underwent CABG surgery (29). However, among the 2,438 patients enrolled with STEMI within 12 h undergoing primary PCI, the 30-day hazard reduction with prasugrel was less than in the 1,094 randomized patients with a recent STEMI within 14 days (0.92 vs. 0.50, respectively), possibly due to the fact that most patients received both thienopyridine agents for the first time at or after the time of the PCI procedure (29). A comparison between a 600-mg clopidogrel loading dose and a prasugrel 60-mg loading dose initiated as early as possible (e.g., in the ambulance or emergency room) in patients with STEMI undergoing primary PCI has not been performed. The results of the present study do suggest, however, that the dosing and timing of thienopyridine agents before primary PCI may importantly impact clinical outcomes, thus warranting the further evaluation of the efficacy and safety of more potent antiplatelet agents in STEMI.

Several caveats of the present report should be acknowledged. As an observational (though pre-specified) analysis of the HORIZONS-AMI trial, the results should be confirmed in dedicated randomized studies. Although the clopidogrel loading dose was stratified before the randomization (ensuring balance of this variable according to anticoagulation regimen), the 300-mg versus 600-mg loading dose itself was not randomized, resulted in imbalance in several baseline, angiographic, and procedural characteristics. Despite the use of multivariable and propensity score analysis to correct for these differences in measured confounders, it is unknown whether unmeasured confounders are present that may have affected the results. A previous study has suggested that matching according to the propensity score eliminates a greater proportion of baseline differences between 2 treatments than does stratification or covariate adjustment (30). Nevertheless, the propensity score matching technique cannot entirely adjust for unmeasured patient characteristics that might influence assignment to the clopidogrel treatment group. Finally, the impact of clopidogrel resistance and potential drug-drug interactions such as between clopidogrel and proton pump inhibitors were not evaluated in the present study (31,32).

Conclusions

In the large-scale, multicenter HORIZONS-AMI trial, a 600-mg loading dose of clopidogrel was associated with lower rates of 30-day mortality, reinfarction, subacute stent thrombosis, and composite MACE compared with a 300 mg loading dose, without increase rates of bleeding in patients with STEMI undergoing primary PCI. Compared with UFH plus a GPI, the clinical benefits of bivalirudin monotherapy (less bleeding and NACE, similar MACE) were independent of the loading dose of clopidogrel, although the overall adverse event rates were lower after a 600-mg loading dose of clopidogrel compared with a 300-mg dose with both anticoagulation regimens. Pending further studies, these data suggest that the use of 600 mg of clopidogrel as the loading dose of choice in patients with STEMI undergoing primary PCI is safe and more efficacious than 300 mg.

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